The Increased Biological Effectiveness of Heavy Charged Particle Radiation:

From Cell Culture Experiments to Biophysical Modelling

Michael Scholz

GSI Darmstadt

Ion Beams for Tumor Therapy

Advantage of ion beams for therapy:

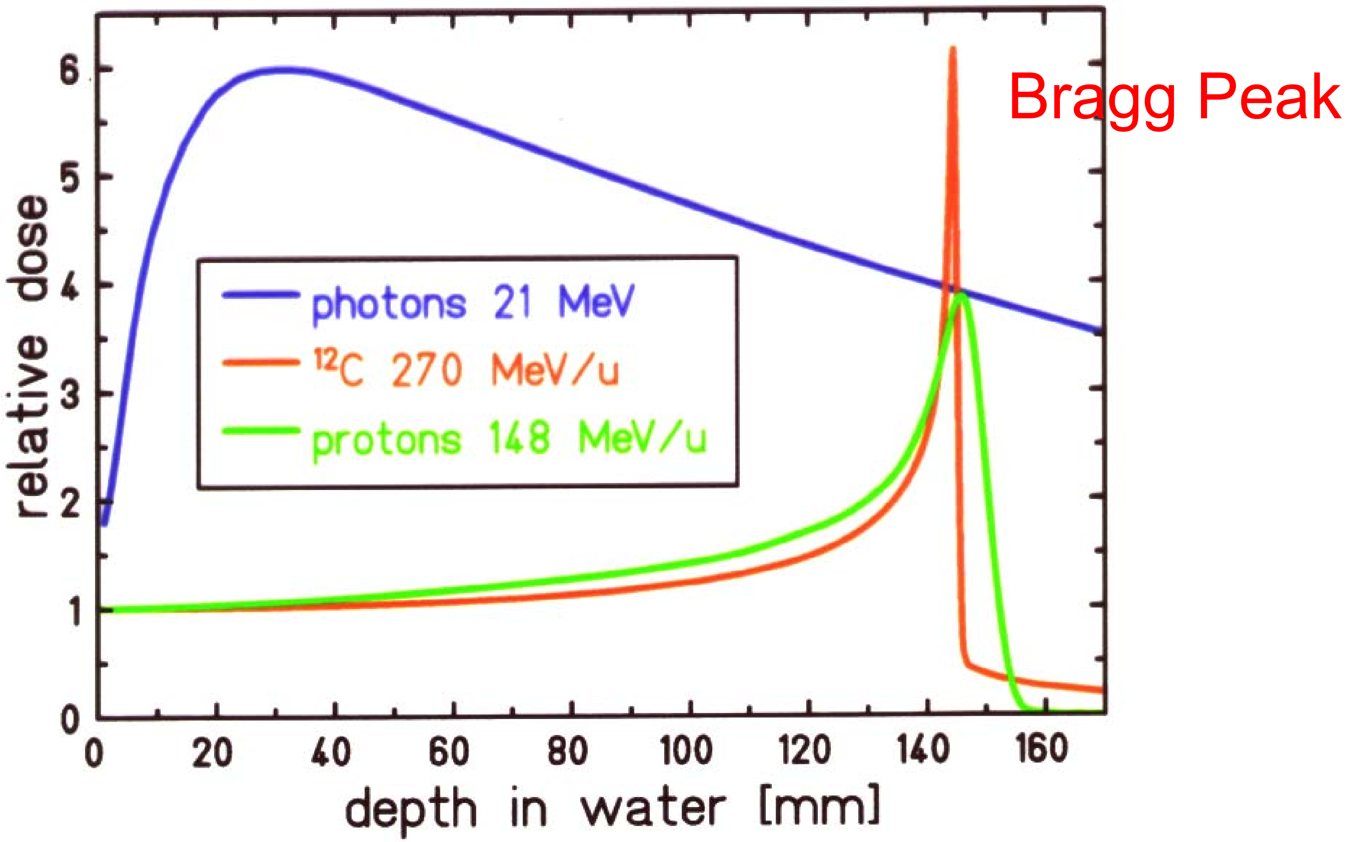
Physical aspects:

- Inverted depth dose profile
- Defined penetration depth
- Reduced lateral scattering

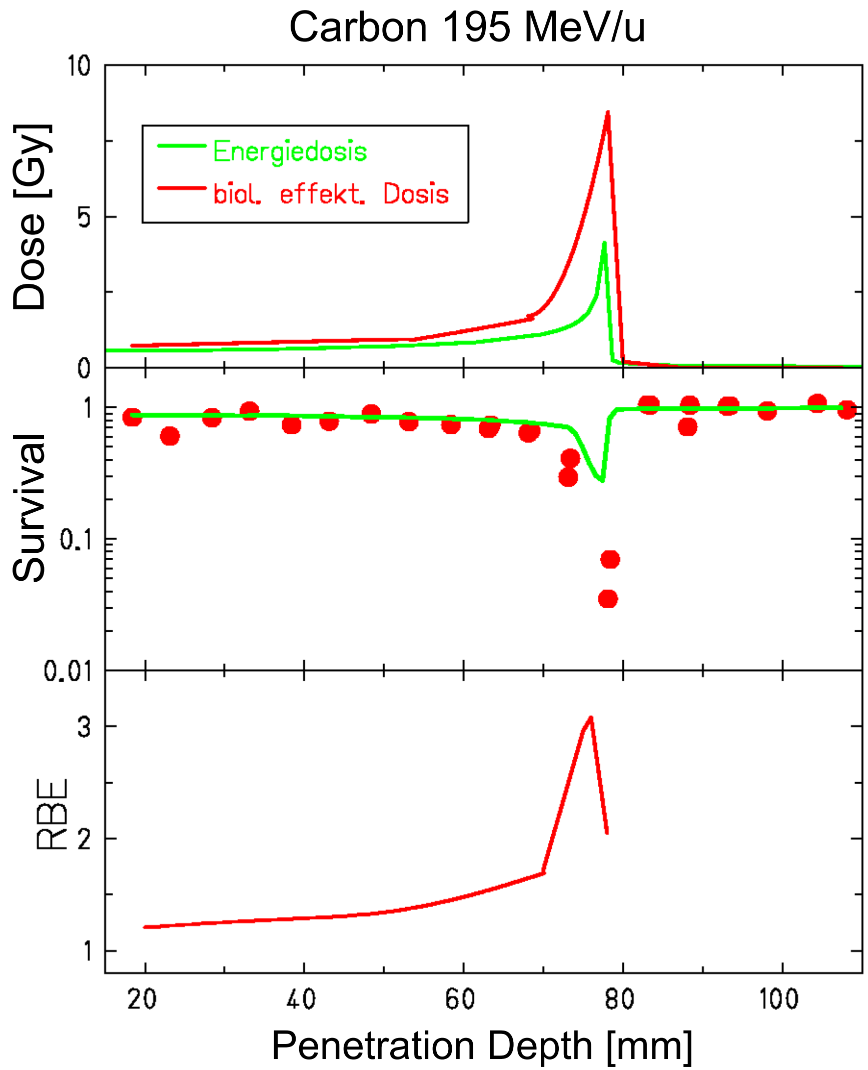
Biological aspects:

- Increased effectiveness
- Reduced oxygen effect

Inverted Depth Dose Profile



Biological Advantage: Increased Effectiveness

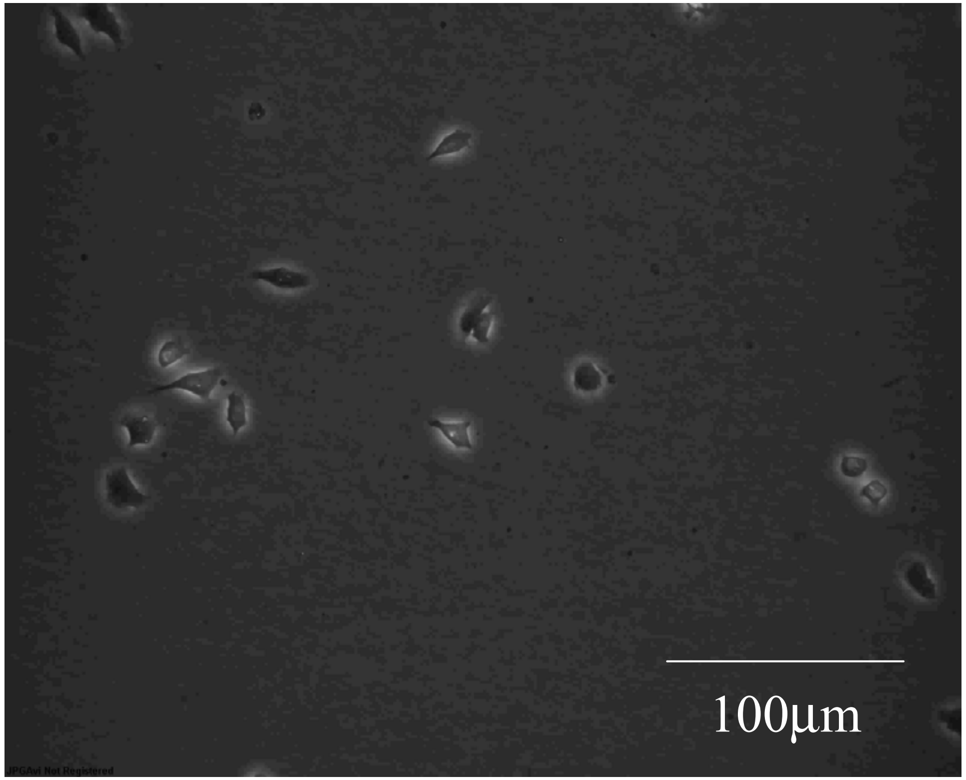


Differential Effect:

RBE(Depth)
>
RBE(Entrance)

Cell Survival

V79 Chinese Hamster Cells



G. Böhrnsen/
I. Katayama

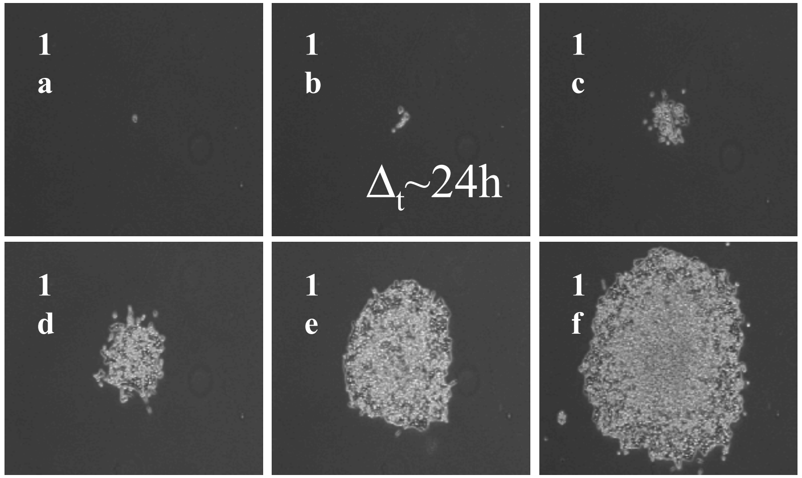
Δt=15min
T_{ges}=85h

Survivor:

1 cell (t=0) ⇨ ≥ 50 cells (t=7d)

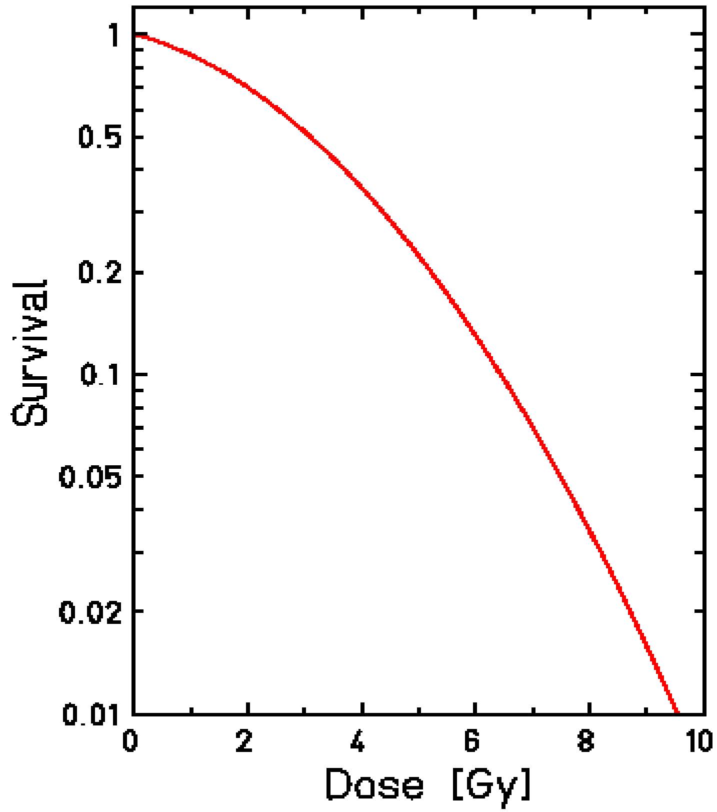
„Colony forming“

Survival after Photon Irradiation



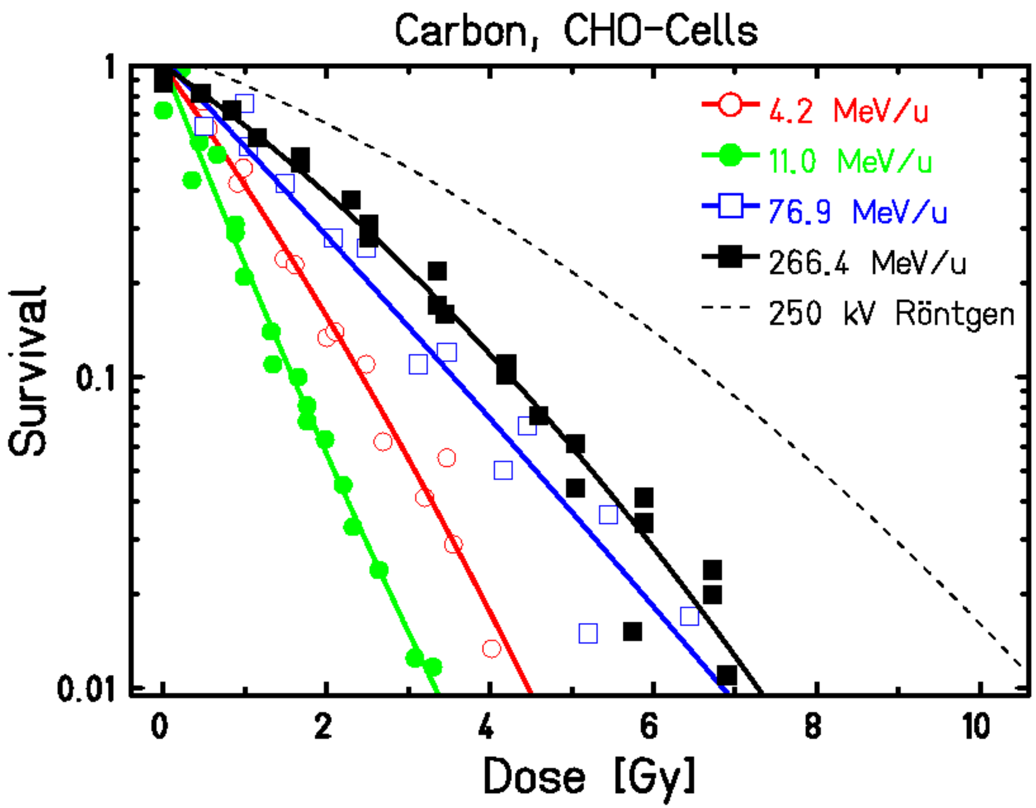
G. Böhrnsen

$$S = \frac{N_{col}}{N_{seed}} = e^{-(\alpha D + \beta D^2)}$$



Shoulder ⟺ Repair

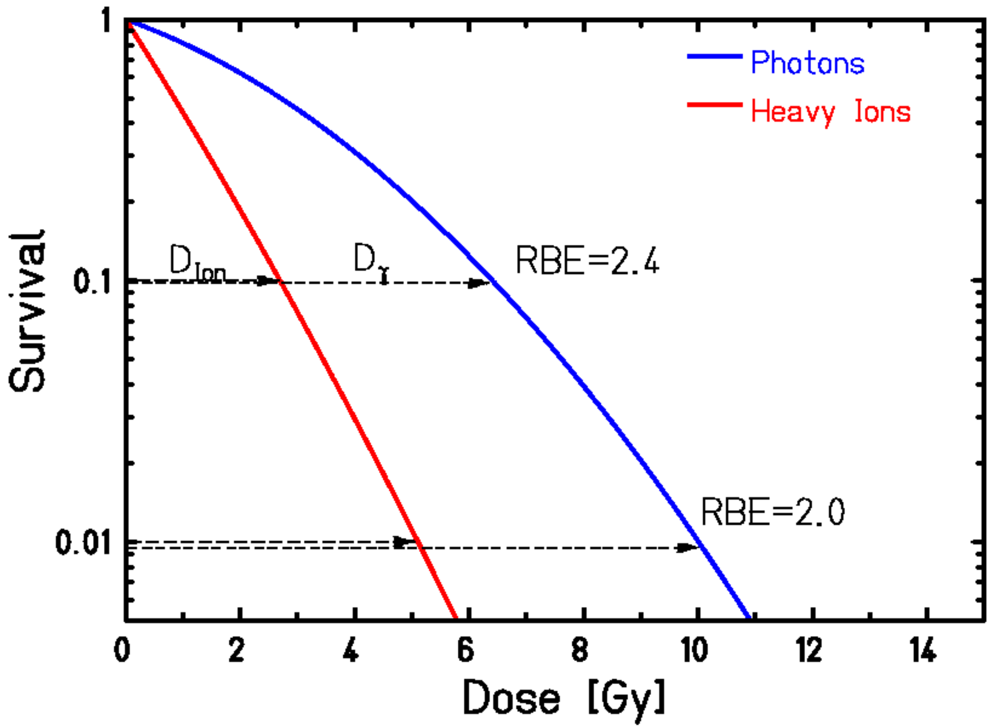
Survival after Carbon Ion Irradiation



W. Kraft-Weyrather

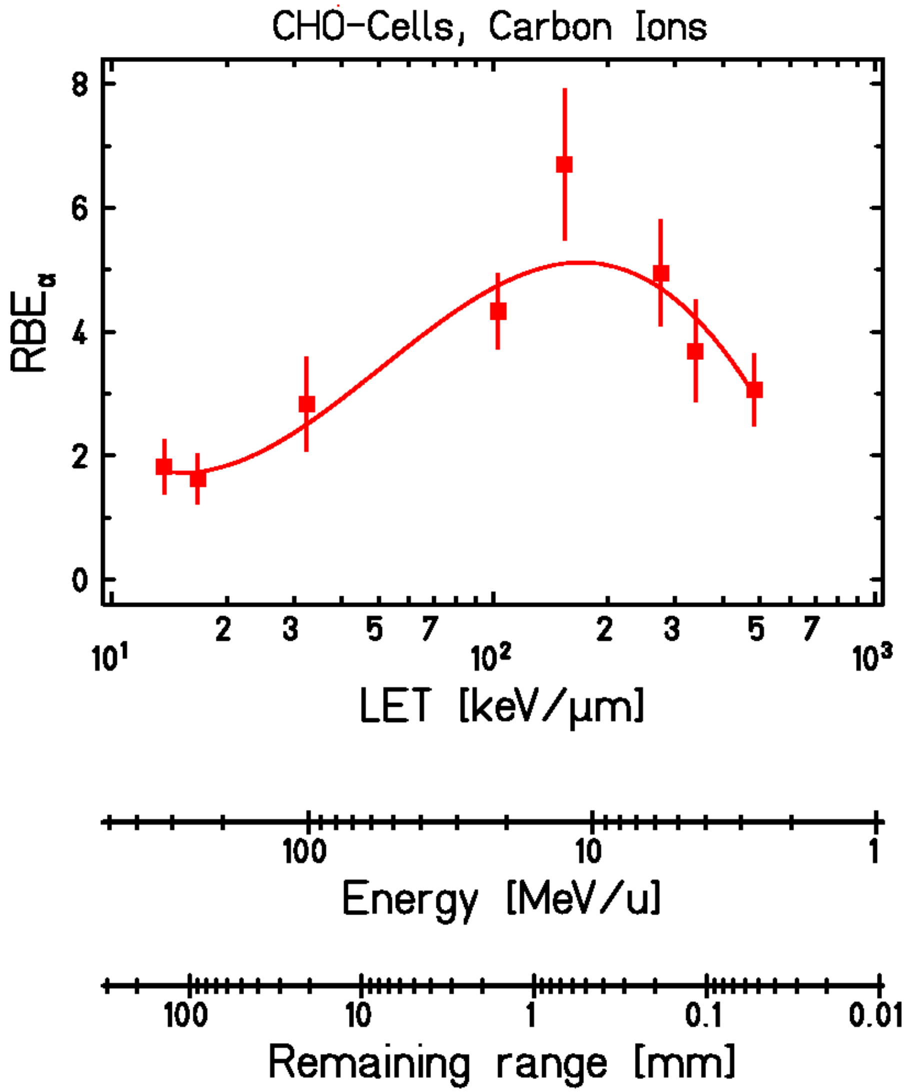
- Increasing effectiveness with decreasing energy
- Saturation effects at very low energies (<10 MeV/u)
- Transition from shouldered to straight survival curves

Definition of Relative Biological Effectiveness



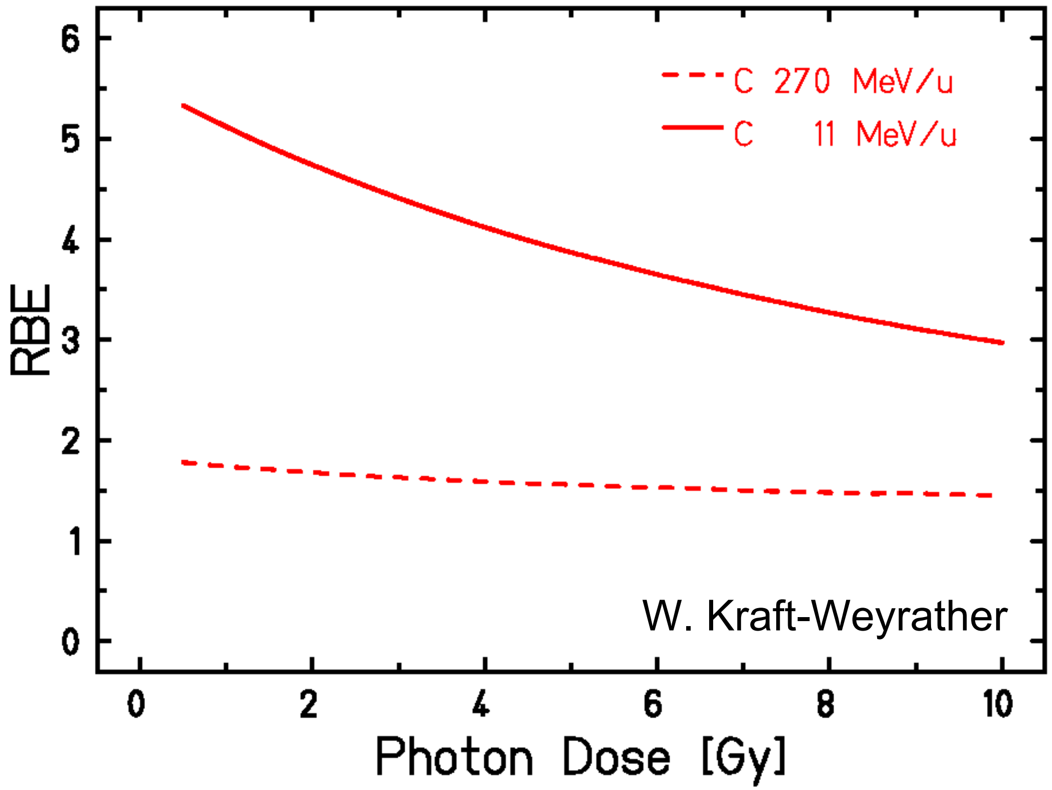
$$RBE = \left. \frac{D_\gamma}{D_{Ion}} \right|_{Isoeffect}$$

RBE depends on LET



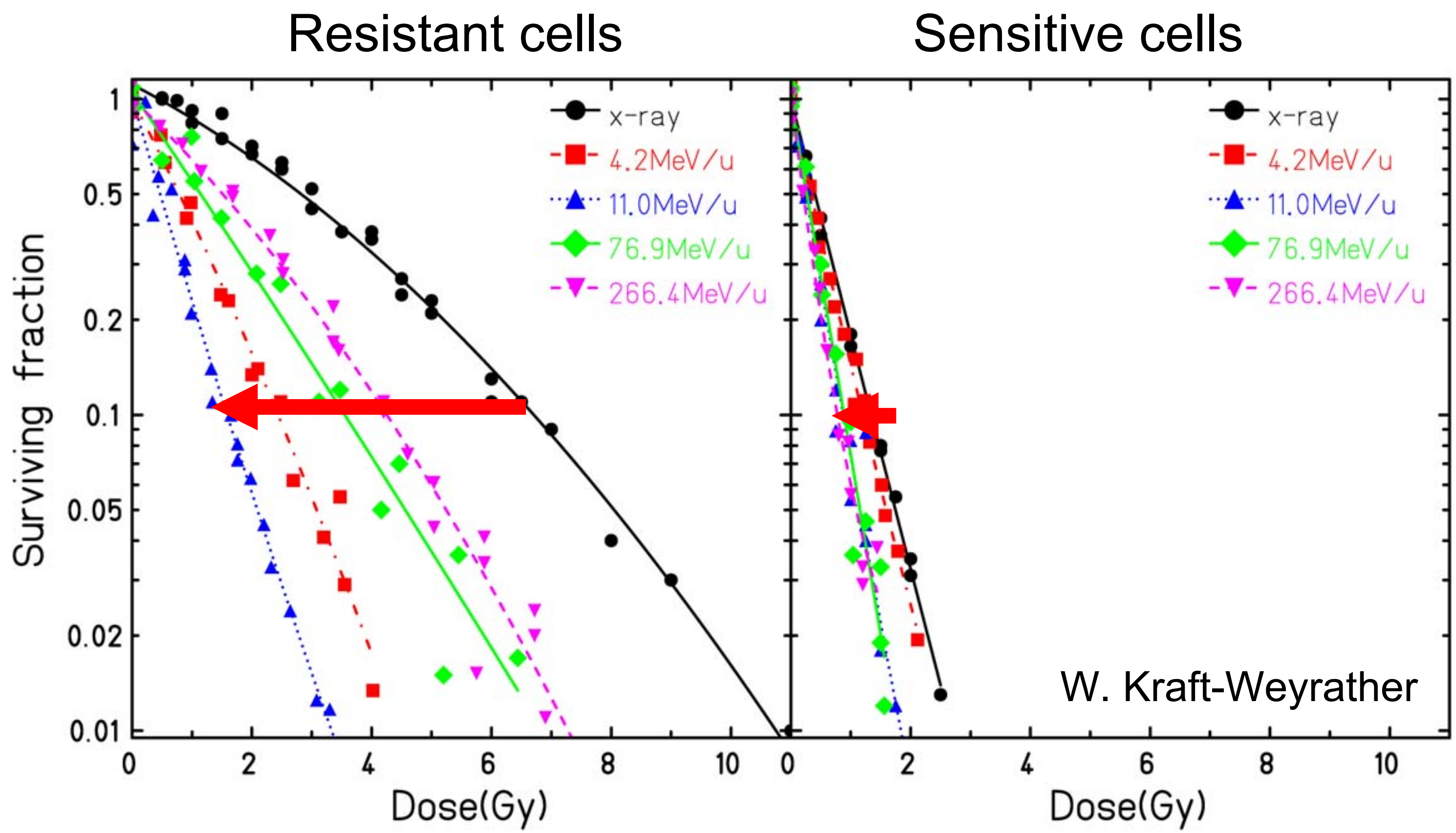
W. Kraft-Weyrather

RBE depends on **Dose**



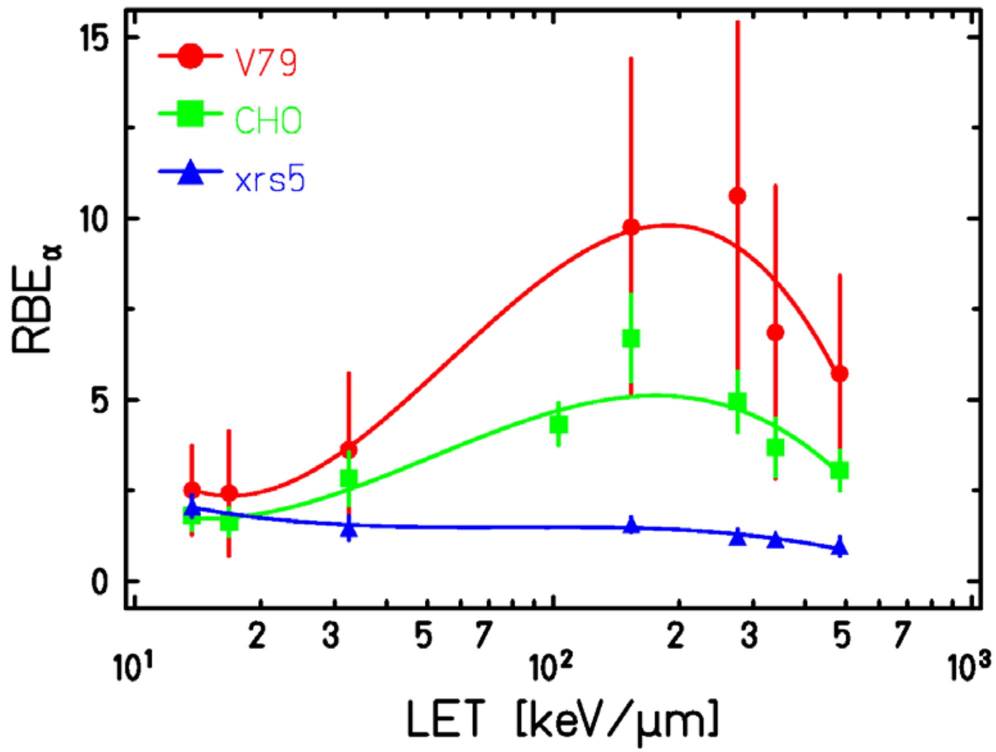
- RBE decreases with dose
- Dose dependence more pronounced for lower energies

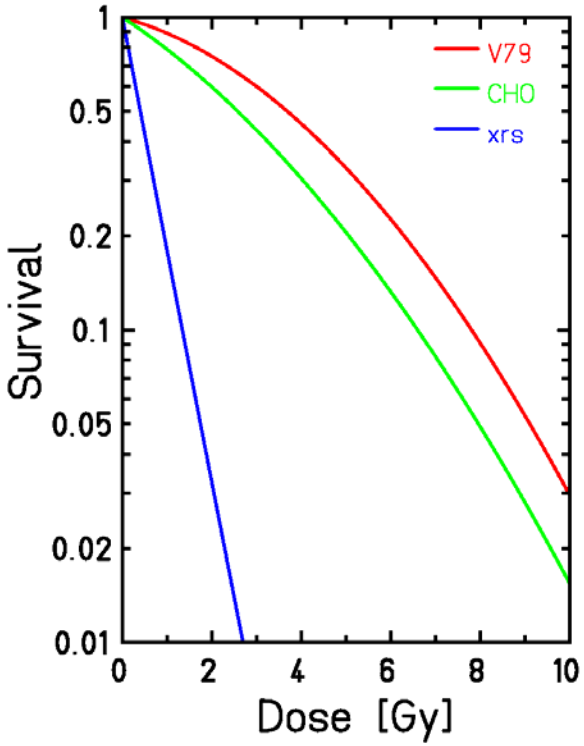
RBE depends on **Cell Type**



Increase of effectiveness is more pronounced for resistant tumors compared to sensitive tumors

RBE depends on **Cell Type**

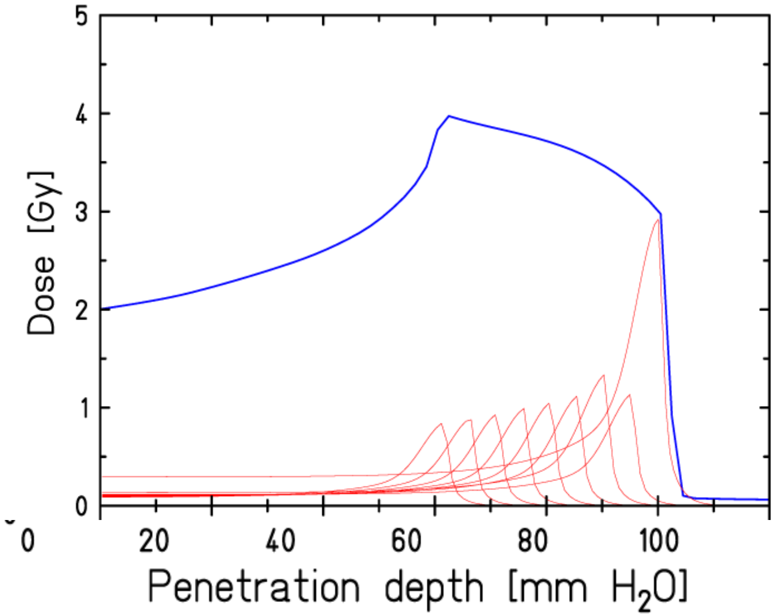


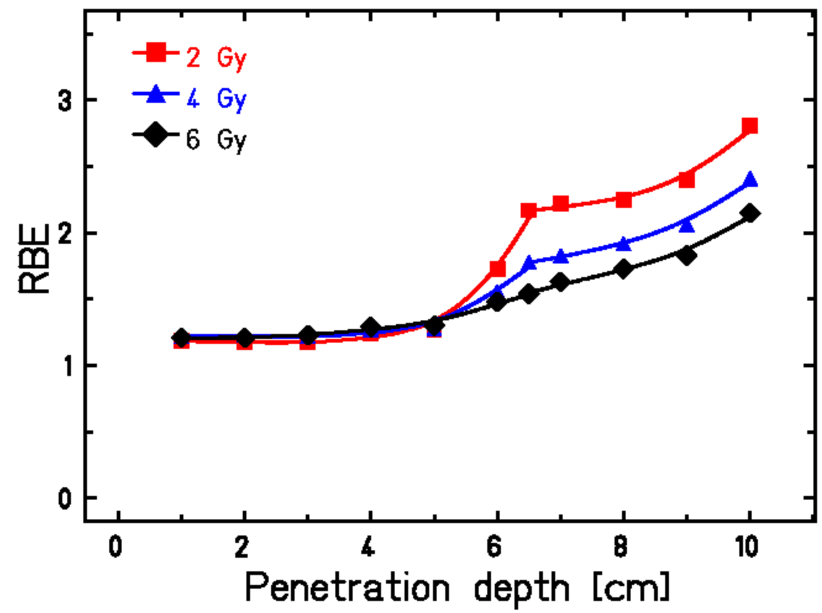


W. Kraft-Weyrather

RBE is higher for resistent (repair proficient) cell types

RBE depends on **Depth**

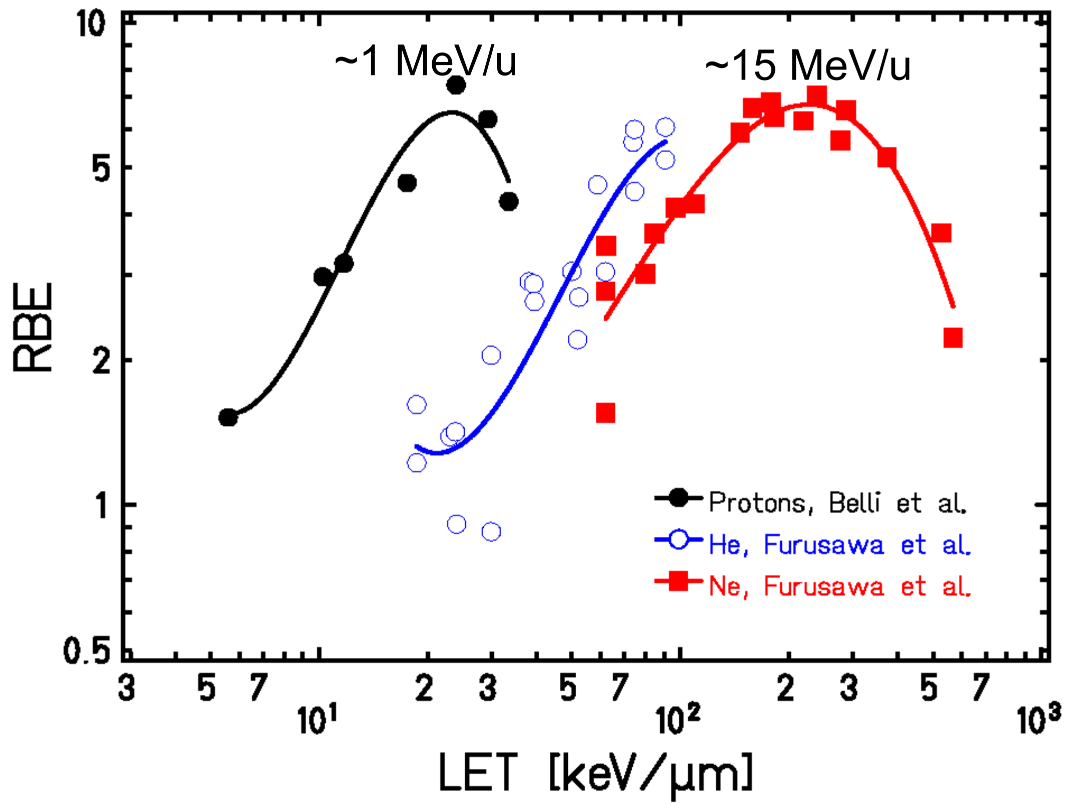




W. Weyrather et al.

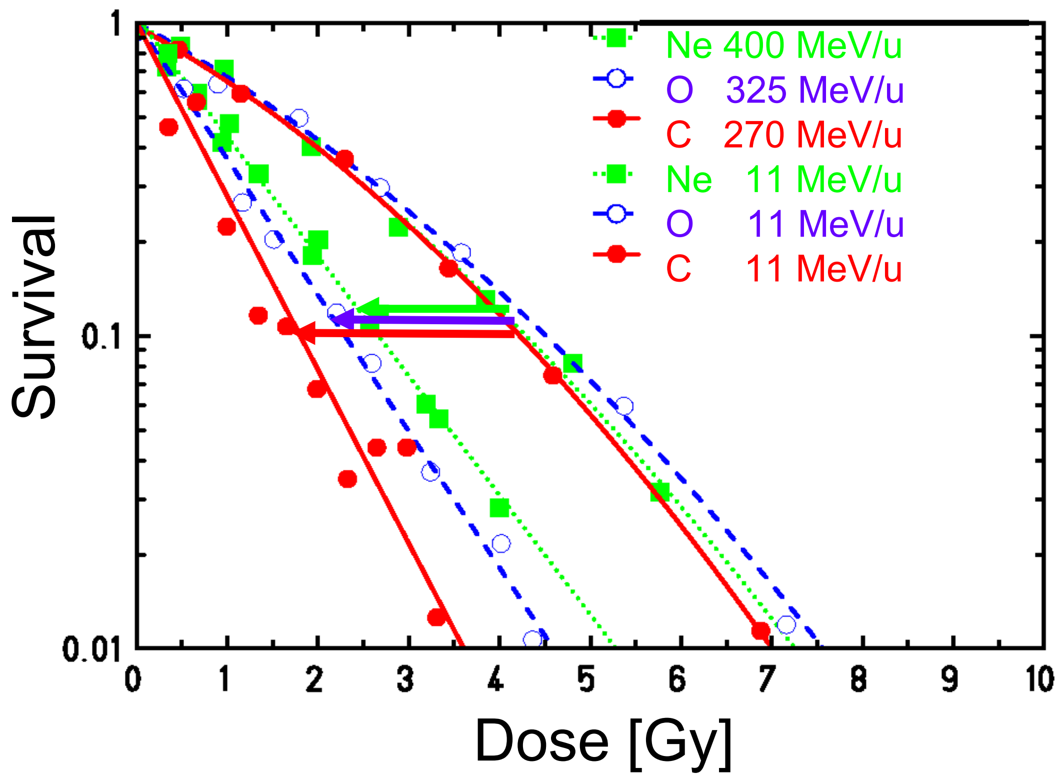
Extended Bragg peak / SOBP irradiation:
Distal part: mainly Bragg peak ions ⇨ high RBE
Proximal part: mix of Bragg peak and higher energies ⇨ moderate RBE

RBE depends on **Ion Species**



- RBE maximum is shifted to higher LET for heavier particles
- The shift corresponds to a shift to higher energies

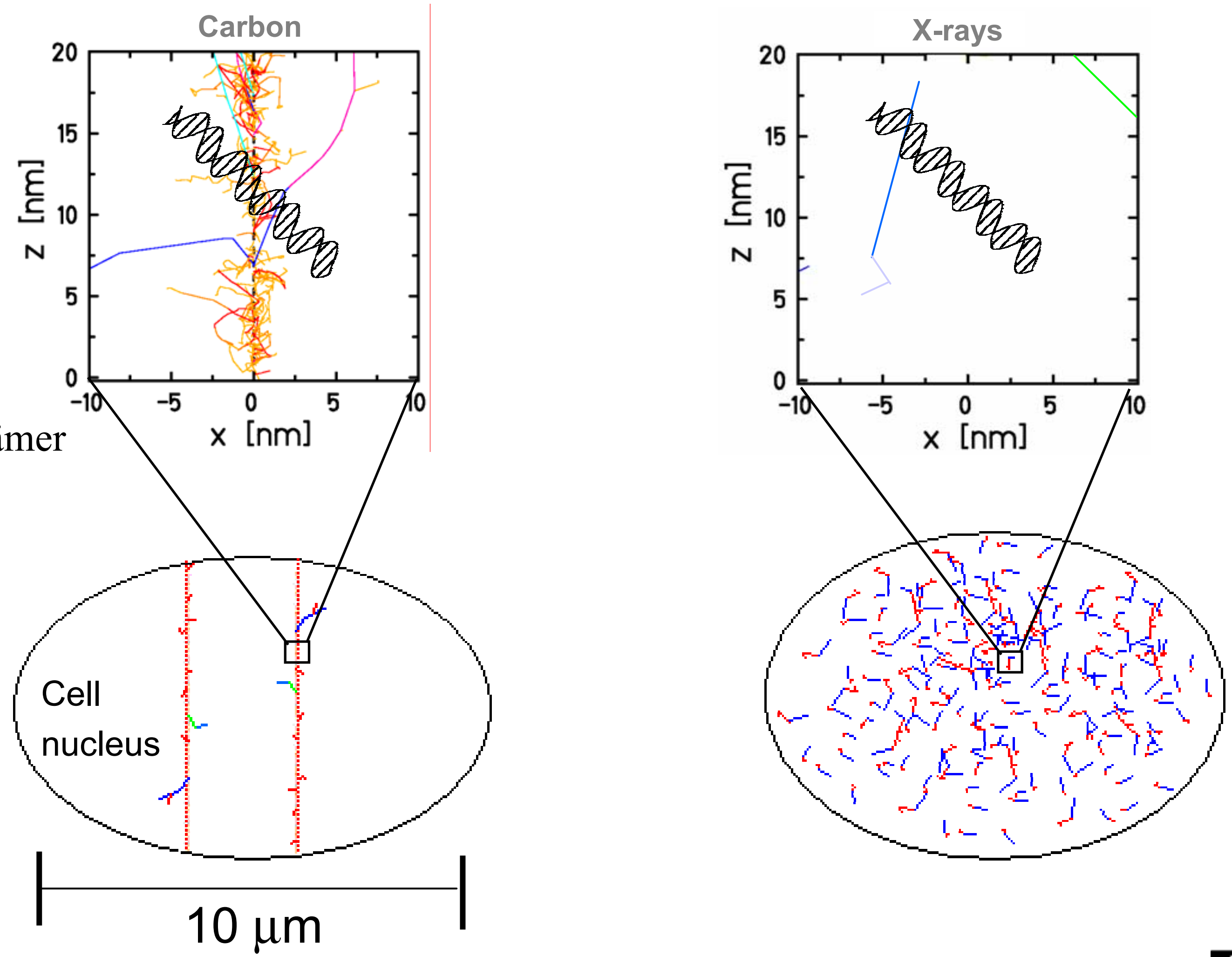
Why Carbon Ions?



W. Kraft-Weyrather

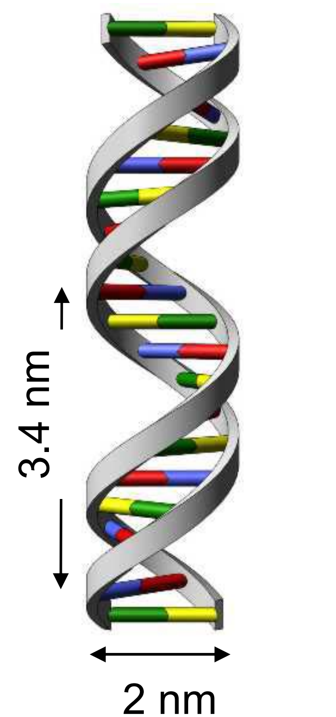
Increase of RBE from entrance channel to Bragg peak region is most pronounced for carbon ions

Explanation of increased effectiveness

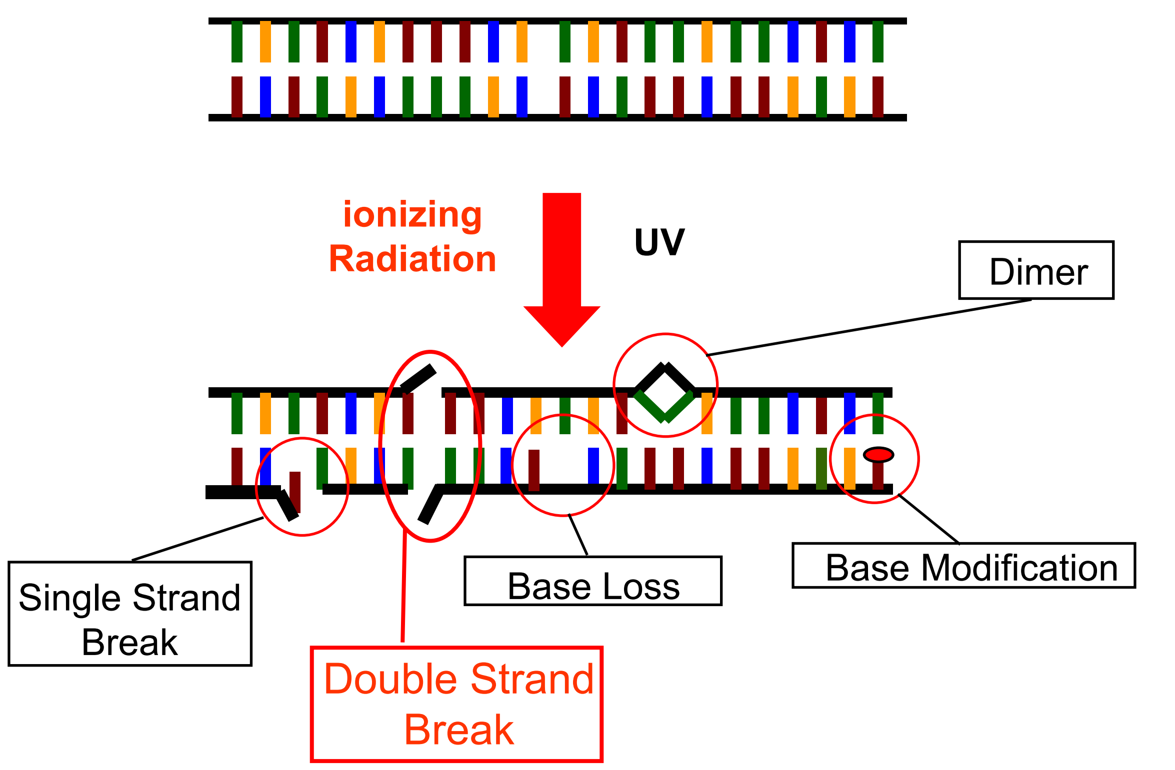


M. Krämer

Radiation induced DNA damage

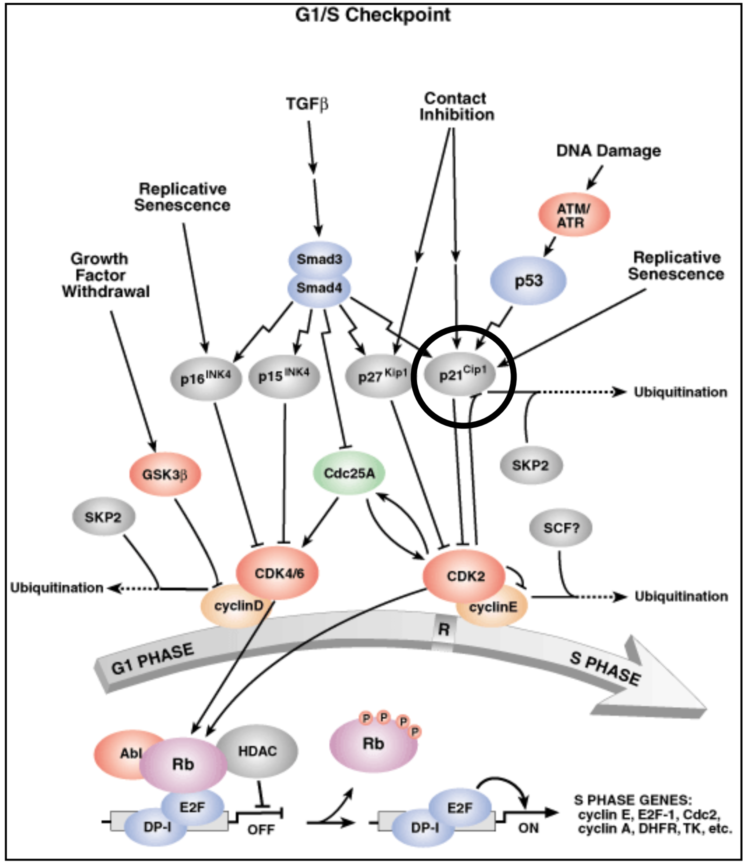


DNA Double Helix

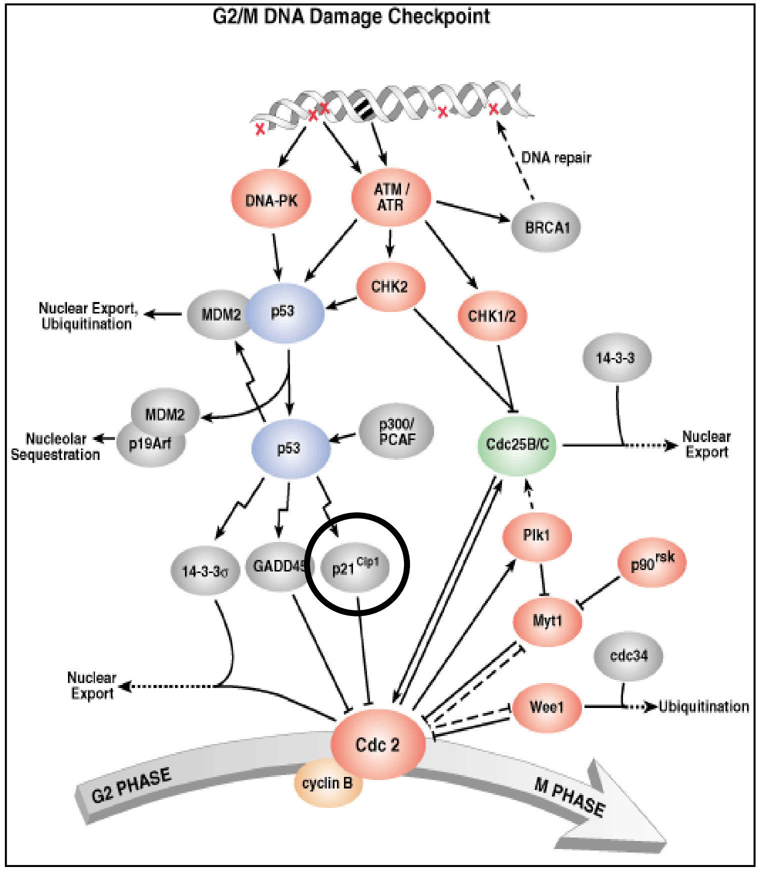


Cells are able to repair radiation induced DNA damage

Cellular Repair Pathways

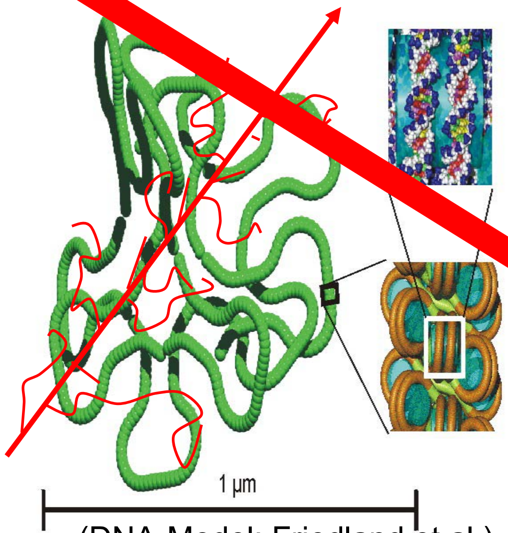


Transition $G_1 \rightarrow$ S-Phase



Transition $G_2 \rightarrow$ M-Phase

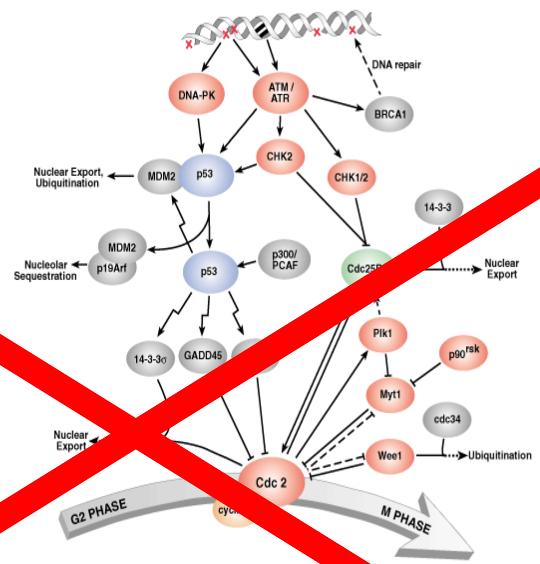
Can we model it from first principles?



(DNA-Model: Friedland et al.)

Initial damage

G2/M DNA Damage Checkpoint

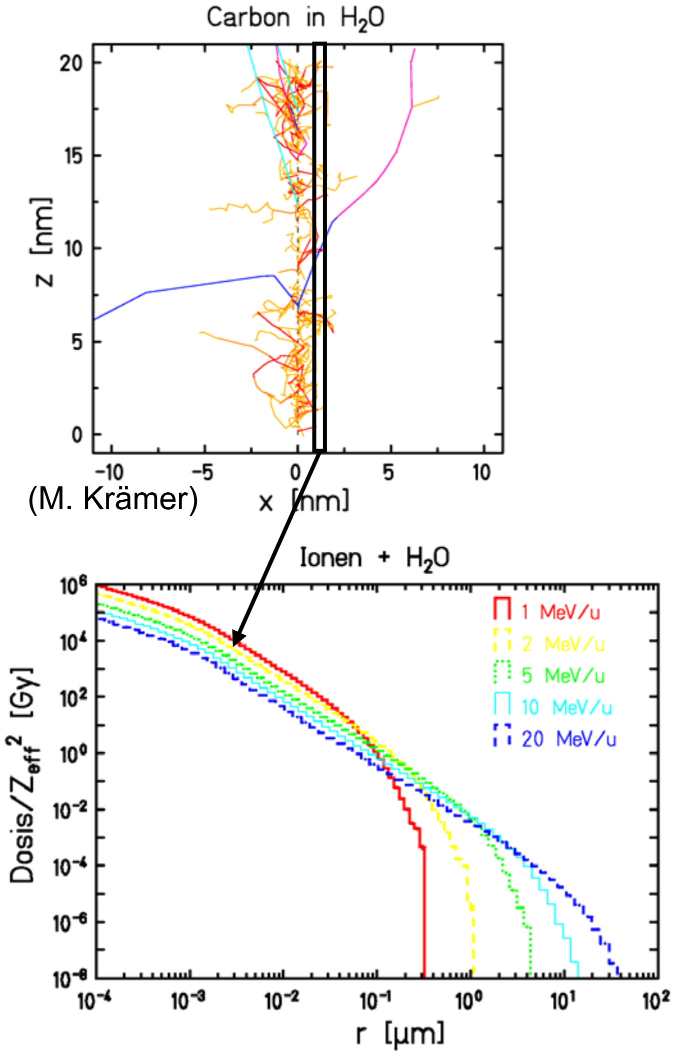


Processing of damage

...

>100 (free?) parameters!
Precision ????

Radial Dose Profile of Particle Tracks

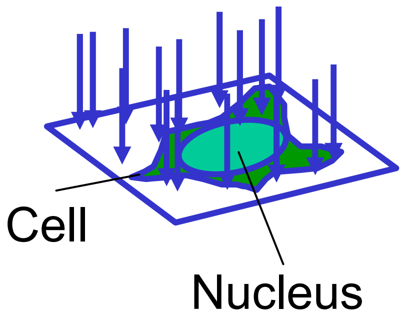


(M. Krämer)

Radial Dose Profile:
D(r): Expectation value

$D(r) \sim 1/r^2$
$R_{Track} \sim E^c$

Microscopic Local Dose Distribution



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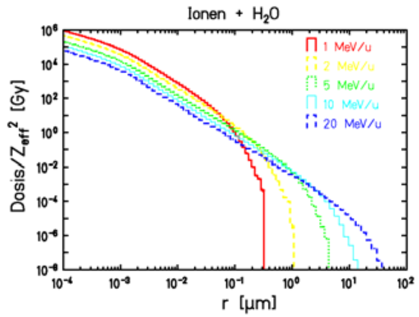
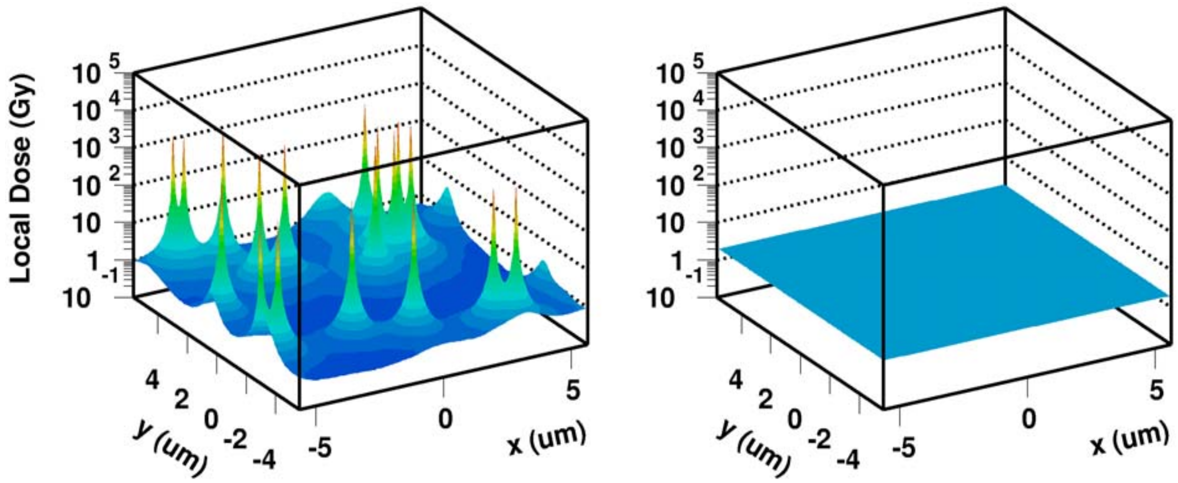
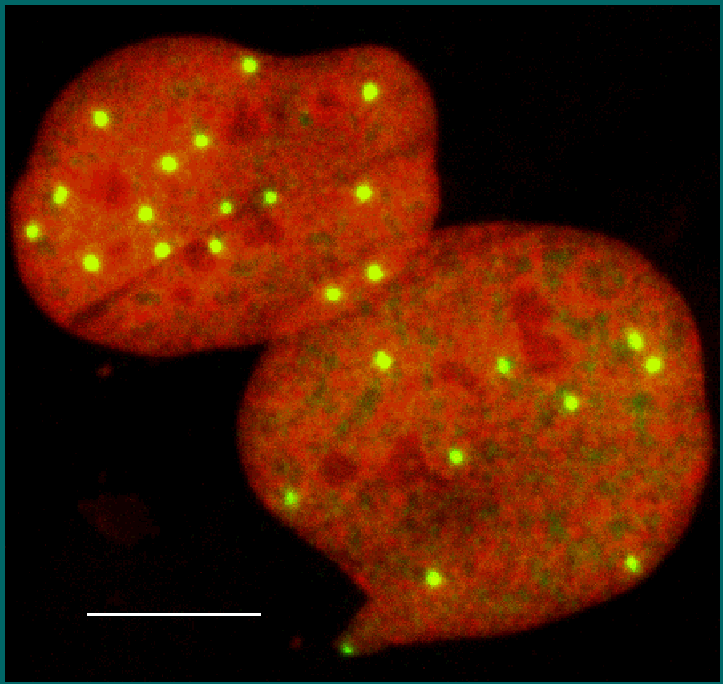




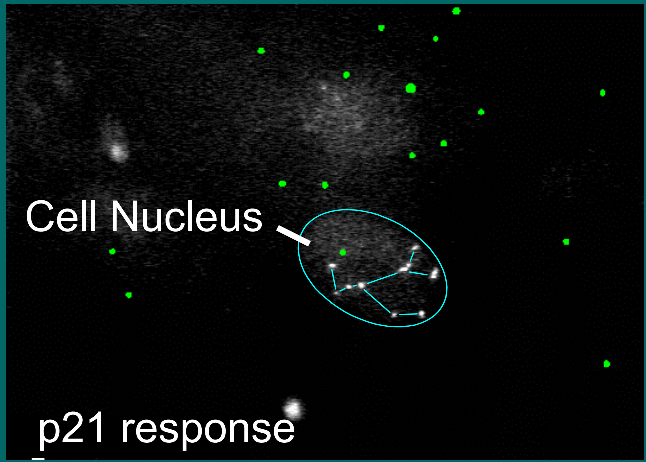
C 15 MeV/u

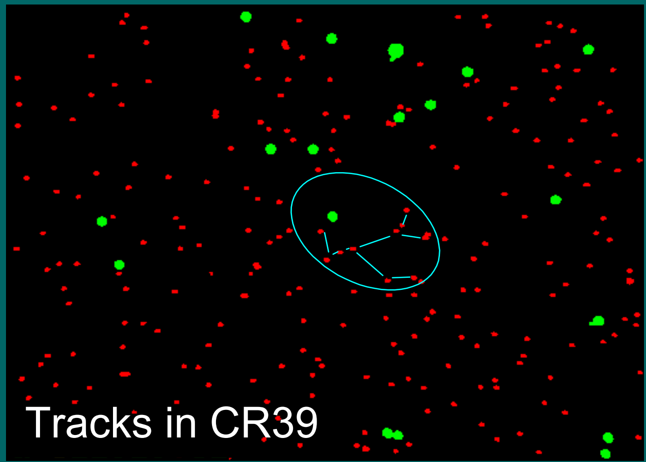
Photons

Visualization of Local Biological Effect



CDKN1A/p21: green
DNA: red
Pb-ions, 3.1 MeV/u, $3x10^6/cm^2$



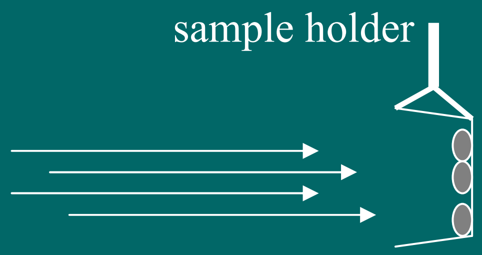


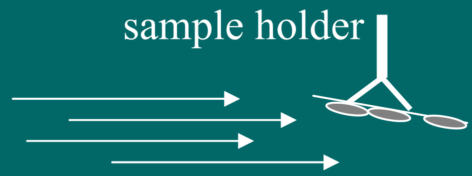
Ca-ions, 10.1 MeV/u, $2x10^6/cm^2$

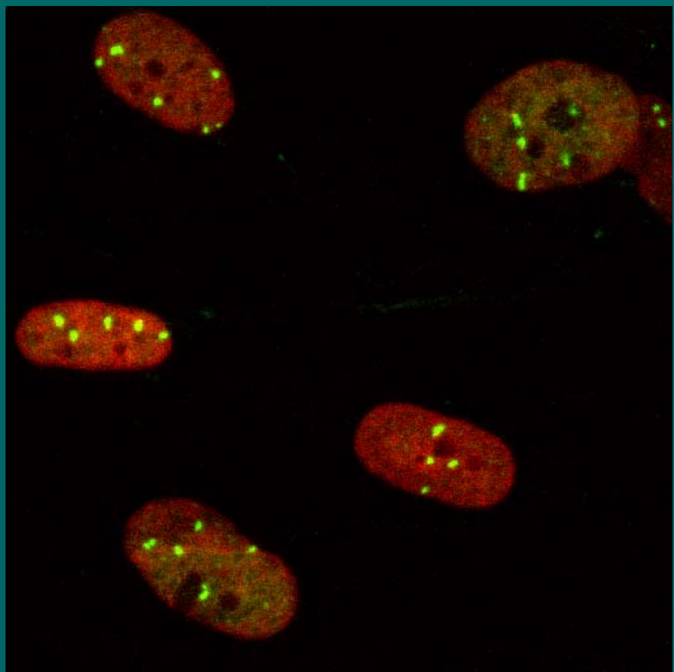
B. Jakob et al.

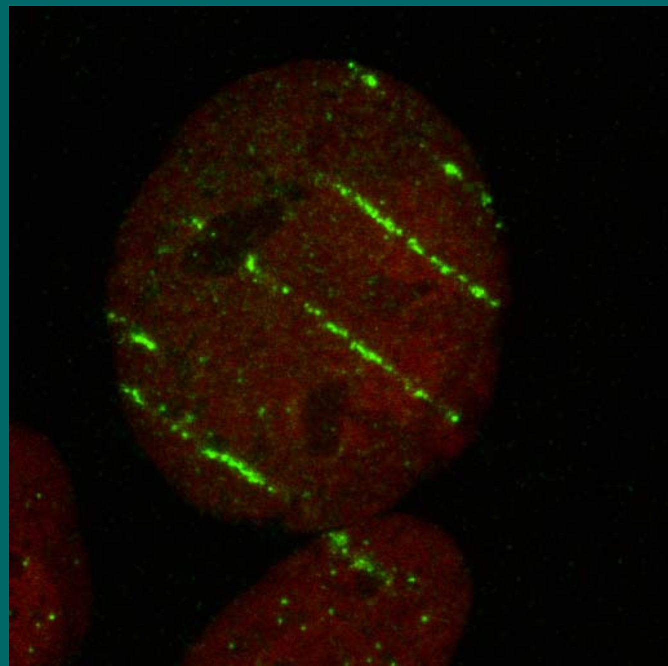
M. Scholz et al.

Biological Visualization of Particle Tracks





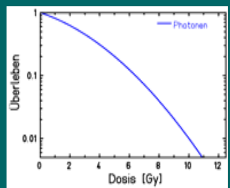




B. Jakob et al.

Amorphous Track Structure Models

<u>Basic Assumption</u>:
Increased effectiveness of particle radiation
can be described by a combination of the
photon dose response and microscopic dose distribution



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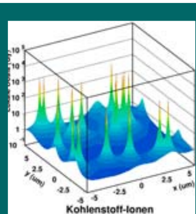


→ RBE !

Principle of Local Effect Model

Local biological effect:

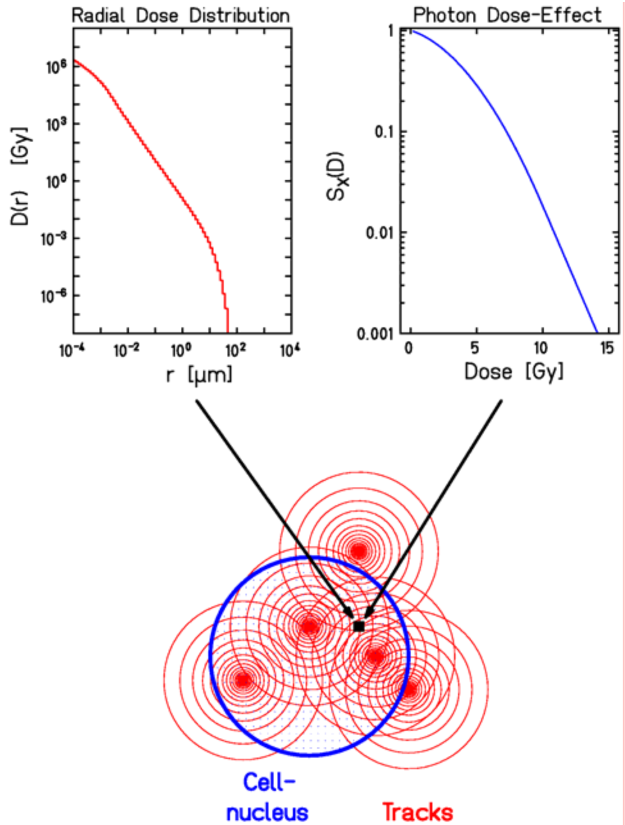
$$S = e^{-\overline{N}_{lethal}}$$

Low-LET dose response:

$$\overline{N}_{lethal}(D) = -\ln S_X(D) = \alpha D + \beta D^2$$

Event density:

$$\nu(D) = \overline{N}_{lethal}(D) / V_{Nucleus}$$



$$\overline{N}_{lethal} = \int \frac{-\ln S_X(d(x,y,z))}{V_{Nucleus}} dV_{Nucleus}$$

M. Scholz et al.

Input Parameters

- Radial Dose Distribution:

  Monte-Carlo (M. Krämer), Analytical Models (Katz, Kiefer), Experimental Data

$$D(r) \propto \frac{1}{r^2} \qquad R_{Track} \propto E^{1.7}$$

- X-ray Survival Curves:

  Experimental data according to LQ; additional assumption: Transition from shoulder to exponential shape at high doses

$$S = e^{-(\alpha D + \beta D^2)}, \quad D < D_t$$

$$S = e^{-s_{\max}(D - D_t)}, \quad D \geq D_t$$

- Target Size (Nuclear Size):

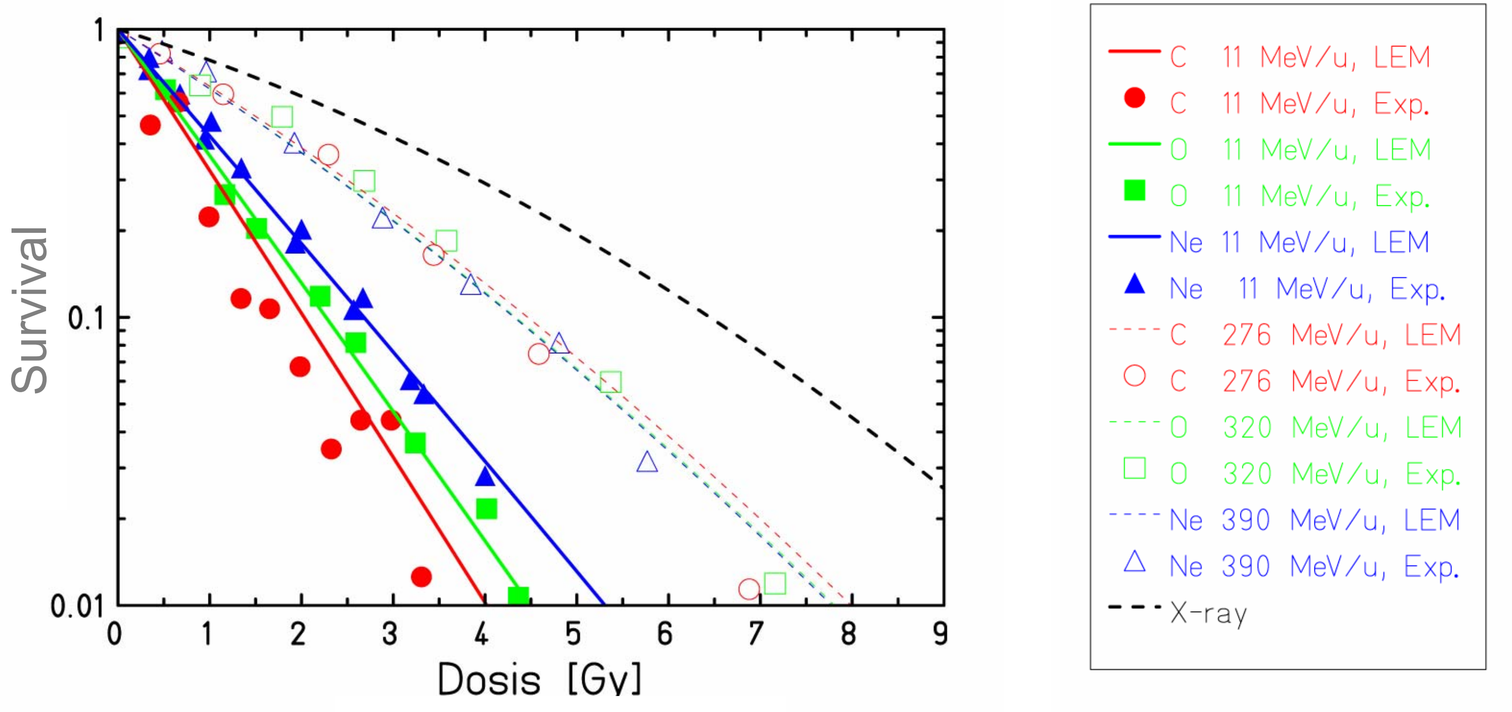
  Experimental Data

Algorithms

- Exact calculation:
  - Monte-Carlo method for determination of ion impact parameters
  - Numerical integration (taking into account overlapping tracks in detail)

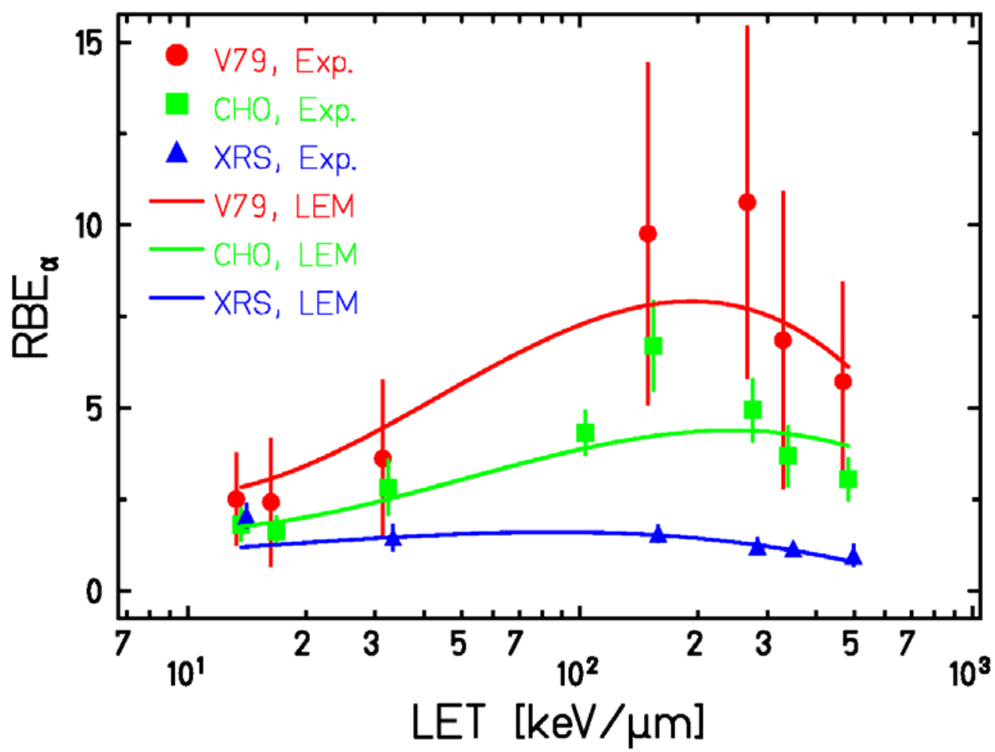
- Approximation:
  - Exact calculation of single particle effects (corresponding to initial slope of survival curve)
  - Estimation of β-term from boundary condition:
    Max. slope of HI curve = max. slope of photon dose response curve

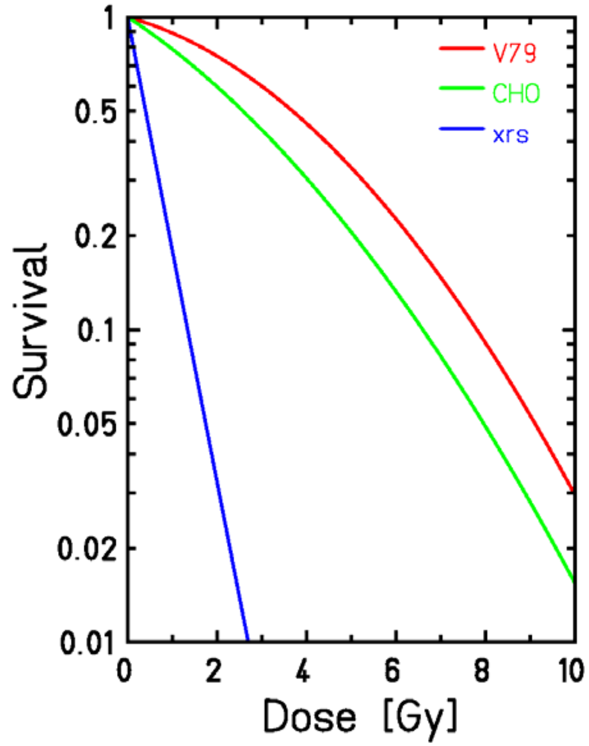
Comparison with experimental data



Data: Kraft-Weyrather et al.

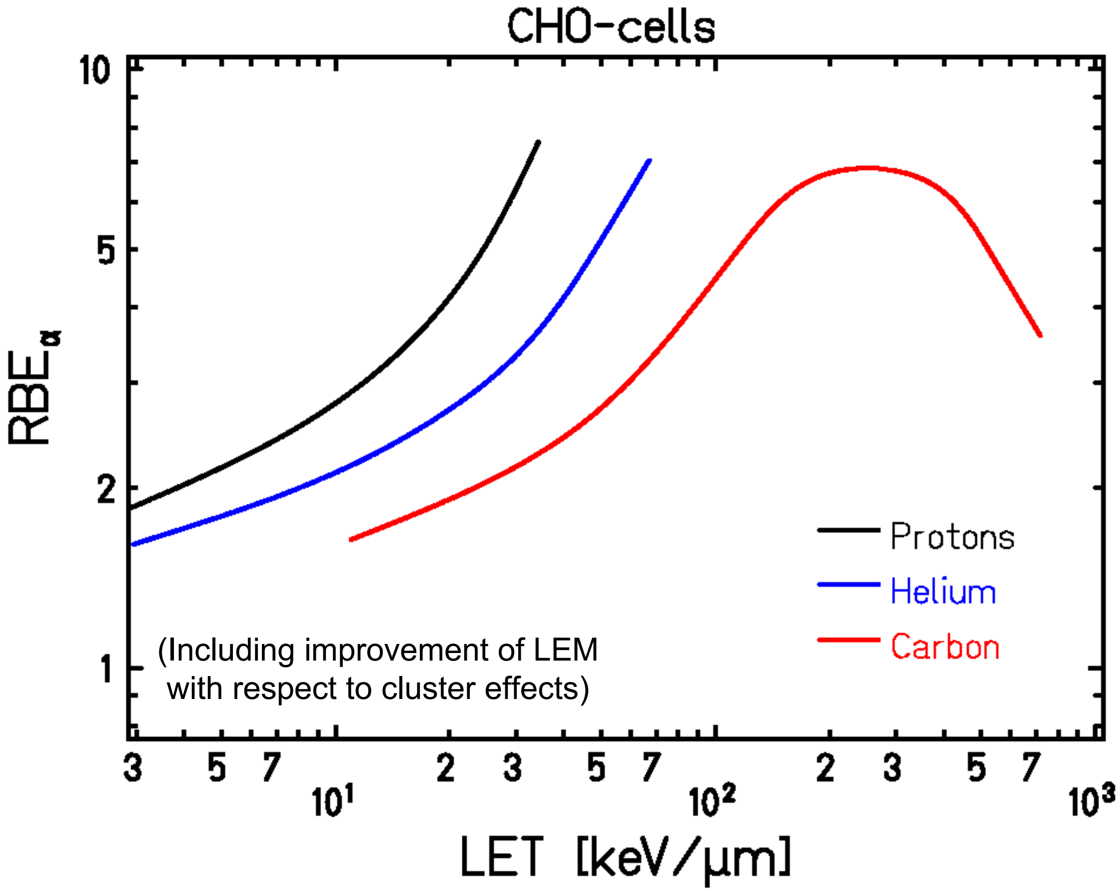
Comparison with experimental data





Data: Weyrather et al., IJRB 1999

Dependence on Particle Species



Influence of track structure; for given LET:

$E(C) > E(He) > E(p)$ ➡ $R_{track}(C) > R_{track}(He) > R_{track}(p)$

Application to Tissue Effects

Tissues show complex response to radiation

↓

Correlation with cell survival?

Nerve tissue: non proliferating cells

↓

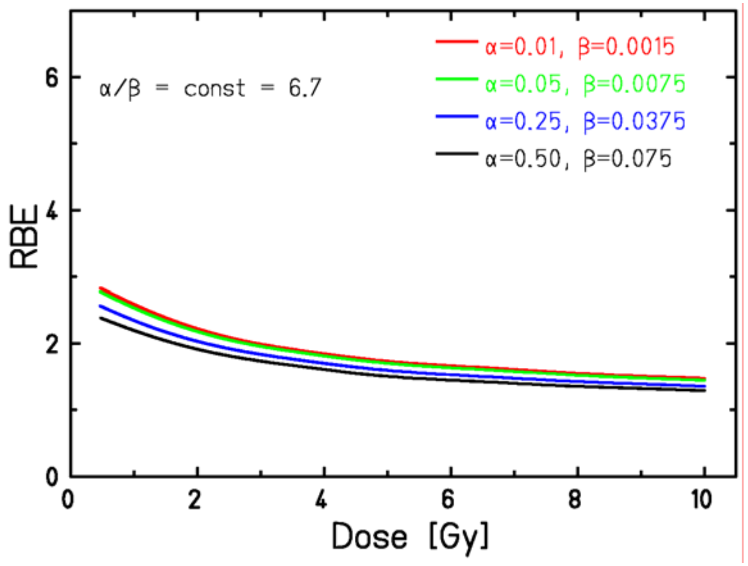
Clonogenic survival not defined

Which parameters of photon dose response define RBE?

Correlation Shoulder – RBE: Theory

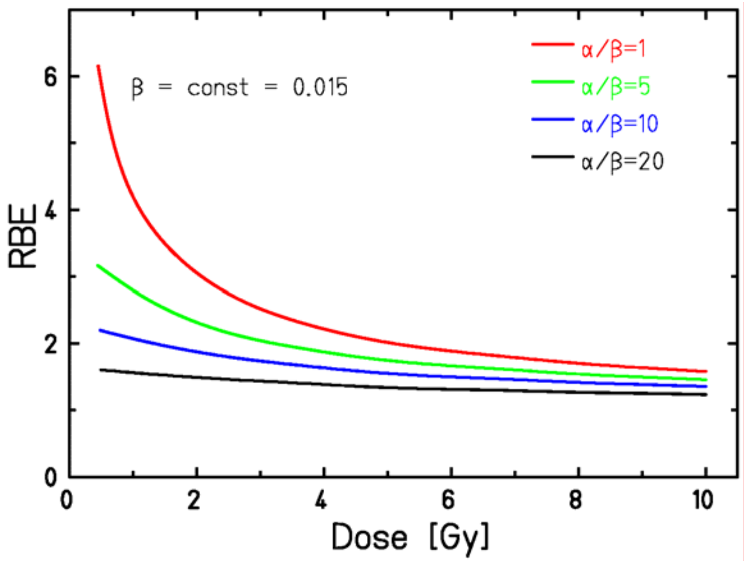
Calculation of mid peak RBE

Carbon 6-10cm SOBP



Constant α_X/β_X-ratio

Varying absolut α_X,β_X values



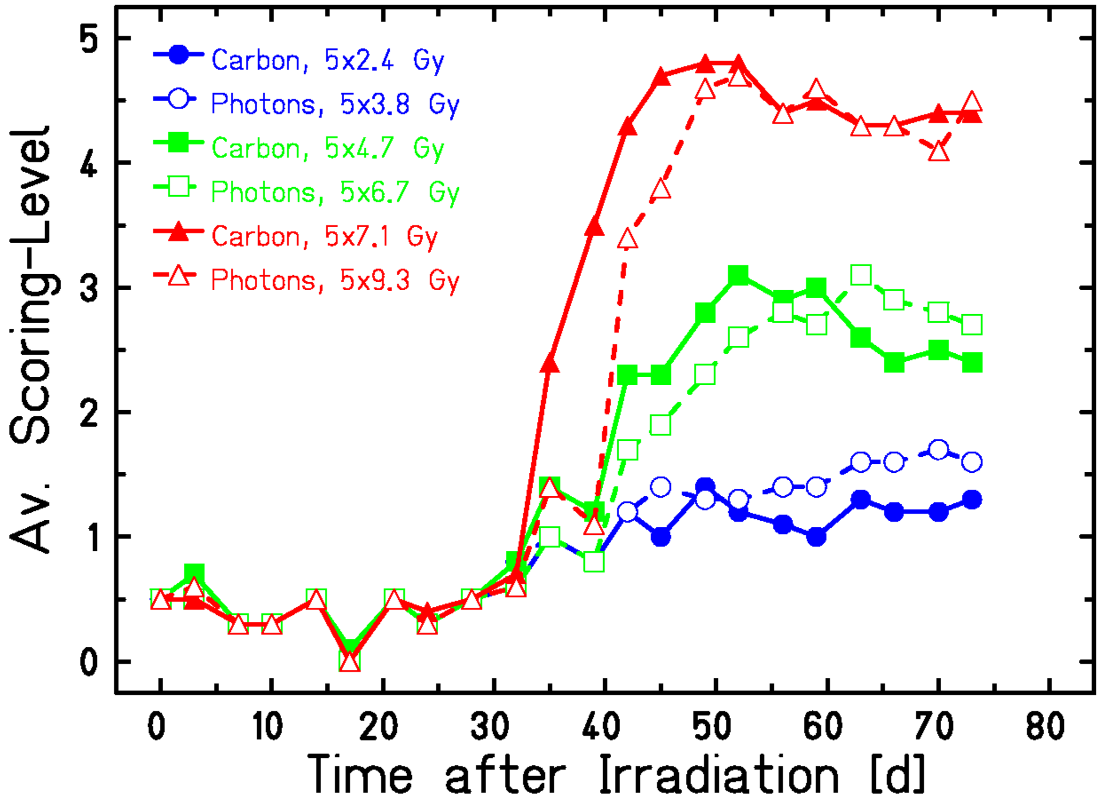
Constant β_X-value

Varying α_X/β_X-ratios

➡ α_X/β_X-ratio determines RBE

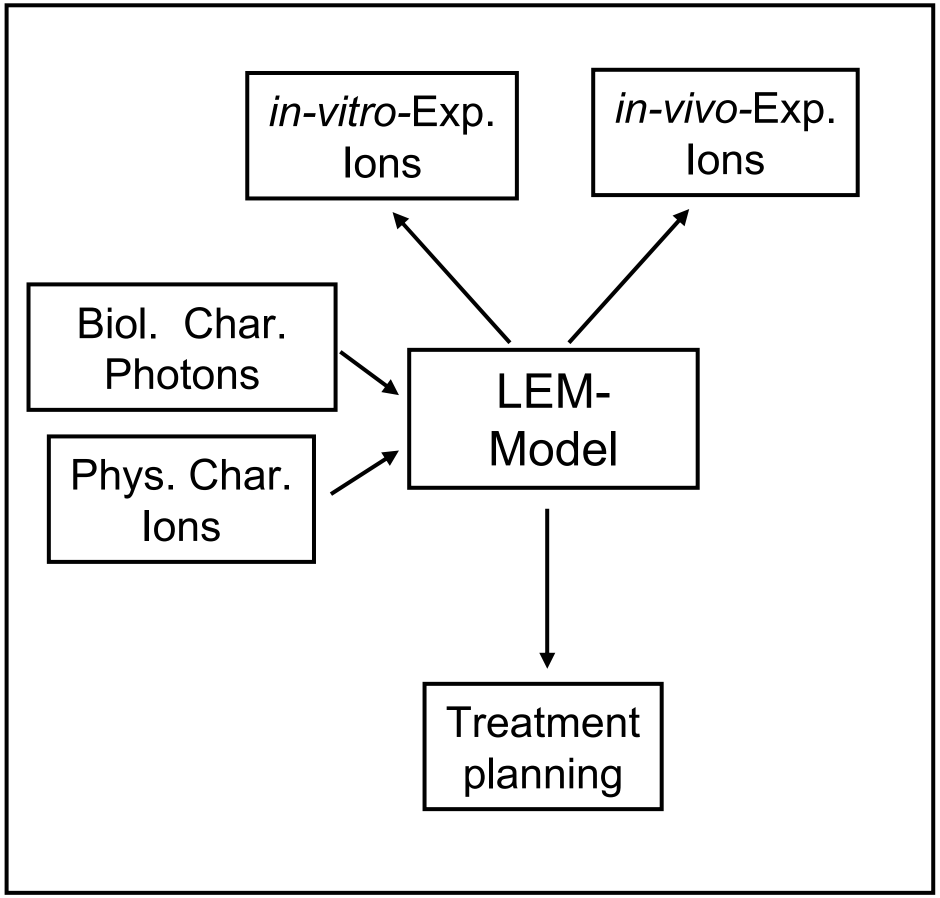
Application to Normal Tissue Effects

Skin reaction in minipigs



Zacharias et al., *Acta Oncol*. 1997

Role of Modeling for Treatment Planning in Heavy Ion Tumor Therapy



Summary

- Biological advantage of ion beams in tumor therapy: increased effectiveness in Bragg peak region
- Increased effectiveness depends on factors like dose, ion species & energy, cell type, ...
- Complex dependencies require modeling for treatment planning in ion tumor therapy
- Modeling cannot be based on first principles
- Empirical approaches based on a link to the photon dose response curves allow high quantitative precision